

**PCT**WORLD INTELLECTUAL PROPERTY ORGANIZATION  
International Bureau

## INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

<b>(51) International Patent Classification <sup>6</sup> :</b> <b>A61K 9/08, 9/10, 47/10, 38/04, 38/06, 9/00</b>		<b>A1</b>	<b>(11) International Publication Number:</b> <b>WO 97/46222</b> <b>(43) International Publication Date:</b> 11 December 1997 (11.12.97)
<b>(21) International Application Number:</b> PCT/US97/09109 <b>(22) International Filing Date:</b> 30 May 1997 (30.05.97)  <b>(30) Priority Data:</b> 60/019,097      3 June 1996 (03.06.96)      US 9613109.9      21 June 1996 (21.06.96)      GB  <b>(71) Applicant (for all designated States except US):</b> MERCK & CO., INC. [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065 (US).  <b>(72) Inventors; and</b> <b>(75) Inventors/Applicants (for US only):</b> OSTOVIC, Drazen [HR/US]; 126 East Lincoln Avenue, Rahway, NJ 07065 (US). THOMPSON, Karen, C. [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065 (US).  <b>(74) Common Representative:</b> MERCK & CO., INC.; 126 East Lincoln Avenue, Rahway, NJ 07065 (US).			<b>(81) Designated States:</b> AL, AM, AU, AZ, BA, BB, BG, BR, BY, CA, CN, CU, CZ, EE, GE, HU, IL, IS, JP, KG, KR, KZ, LC, LK, LR, LT, LV, MD, MG, MK, MN, MX, NO, NZ, PL, RO, RU, SG, SI, SK, TJ, TM, TR, TT, UA, US, UZ, VN, YU, ARIPO patent (GH, KE, LS, MW, SD, SZ, UG), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).  <b>Published</b> <i>With international search report. Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i>
<b>(54) Title:</b> PEDIATRIC FORMULATION FOR HIV PROTEASE INHIBITORS			
<b>(57) Abstract</b>  Dispersal or suspension of HIV protease inhibitor in glycerol improves palatability and taste for the preparation of suitable pediatric formulations in the treatment of AIDS, ARC or HIV infection in children and infants.			

**FOR THE PURPOSES OF INFORMATION ONLY**

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
AM	Armenia	FI	Finland	LT	Lithuania	SK	Slovakia
AT	Austria	FR	France	LU	Luxembourg	SN	Senegal
AU	Australia	GA	Gabon	LV	Latvia	SZ	Swaziland
AZ	Azerbaijan	GB	United Kingdom	MC	Monaco	TD	Chad
BA	Bosnia and Herzegovina	GE	Georgia	MD	Republic of Moldova	TG	Togo
BB	Barbados	GH	Ghana	MG	Madagascar	TJ	Tajikistan
BE	Belgium	GN	Guinea	MK	The former Yugoslav Republic of Macedonia	TM	Turkmenistan
BF	Burkina Faso	GR	Greece	ML	Mali	TR	Turkey
BG	Bulgaria	HU	Hungary	MN	Mongolia	TT	Trinidad and Tobago
BJ	Benin	IE	Ireland	MR	Mauritania	UA	Ukraine
BR	Brazil	IL	Israel	MW	Malawi	UG	Uganda
BY	Belarus	IS	Iceland	MX	Mexico	US	United States of America
CA	Canada	IT	Italy	NE	Niger	UZ	Uzbekistan
CF	Central African Republic	JP	Japan	NL	Netherlands	VN	Viet Nam
CG	Congo	KE	Kenya	NO	Norway	YU	Yugoslavia
CH	Switzerland	KG	Kyrgyzstan	NZ	New Zealand	ZW	Zimbabwe
CI	Côte d'Ivoire	KP	Democratic People's Republic of Korea	PL	Poland		
CM	Cameroon	KR	Republic of Korea	PT	Portugal		
CN	China	KZ	Kazakhstan	RO	Romania		
CU	Cuba	LC	Saint Lucia	RU	Russian Federation		
CZ	Czech Republic	LI	Liechtenstein	SD	Sudan		
DE	Germany	LK	Sri Lanka	SE	Sweden		
DK	Denmark	LR	Liberia	SG	Singapore		
EE	Estonia						

## TITLE OF THE INVENTION

### PEDIATRIC FORMULATION FOR HIV PROTEASE INHIBITORS

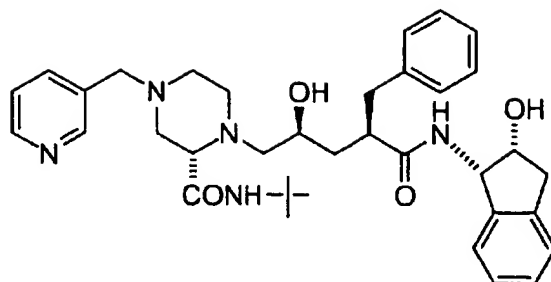
## BACKGROUND OF THE INVENTION

5           A retrovirus designated human immunodeficiency virus (HIV) is the etiological agent of the complex disease that includes progressive destruction of the immune system (acquired immune deficiency syndrome; AIDS) and degeneration of the central and peripheral nervous system. This virus was previously known as  
10   LAV, HTLV-III, or ARV. A common feature of retrovirus replication is the extensive post-translational processing of precursor polyproteins by a virally encoded protease to generate mature viral proteins required for virus assembly and function. Inhibition of this processing prevents the production of normally infectious virus. For  
15   example, Kohl, N.E. *et al.*, Proc. Nat'l Acad. Sci., **85**, 4686 (1988) demonstrated that genetic inactivation of the HIV encoded protease resulted in the production of immature, non-infectious virus particles. These results indicate that inhibition of the HIV protease represents a viable method for the treatment of AIDS and the  
20   prevention or treatment of infection by HIV. See, e.g., U.S. 5,413,999.

          Nucleotide sequencing of HIV shows the presence of a *pol* gene in one open reading frame [Ratner, L. *et al.*, Nature, **313**, 277 (1985)]. Amino acid sequence homology provides evidence that  
25   the *pol* sequence encodes reverse transcriptase, an endonuclease and an HIV protease [Toh, H. *et al.*, EMBO J. **4**, 1267 (1985); Power, M.D. *et al.*, Science, **231**, 1567 (1986); Pearl, L.H. *et al.*, Nature, **329**, 351 (1987)].

          One of the most difficult medical challenges is the treatment  
30   of AIDS or HIV infection in children and infants. HIV protease inhibitors have unsatisfactory and unpleasant taste, e.g., CRIVAN® (trademark of Merck & Co. Inc.), which is a sulfate salt of

- 2 -



Converting the sulfate salt to insoluble free base improves taste and palatability, but oral bioavailability is reduced unacceptably, by a factor of up to about three. Furthermore, adding flavors or sweeteners or glycerol to aqueous solutions of the sulfate salt does not improve palatability. Applicants have unexpectedly found that suspension or dispersion of HIV protease inhibitor particles, e.g., of CRIXIVAN®, in glycerol, substantially improves the palatability of the drug.

#### BRIEF DESCRIPTION OF THE INVENTION

Dispersion or suspension in glycerol of HIV protease inhibitors, or pharmaceutically acceptable salt thereof, improve palatability sufficiently to be suitable as pediatric formulations in the treatment of AIDS, ARL or HIV infection in children and infants.

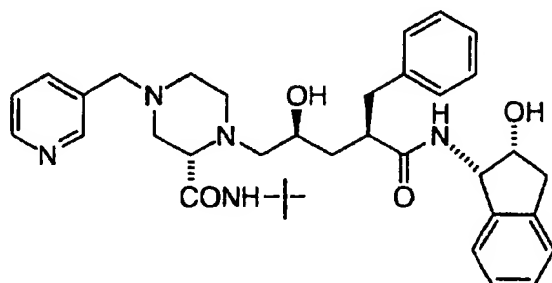
#### ABBREVIATIONS AND DEFINITIONS

q.s. sufficient quantity

#### DETAILED DESCRIPTION OF THE INVENTION

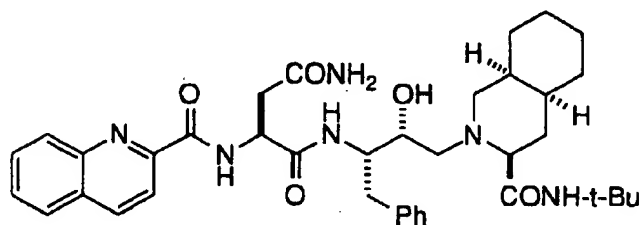
This invention relates to a pediatric formulation of an HIV protease inhibitor, which is a dispersal or suspension of HIV protease inhibitor in a non-toxic, high viscosity, water-miscible liquid, to improve palatability. A preferred liquid is glycerol.

In one embodiment of this invention, the HIV protease inhibitor is the sulfate salt of



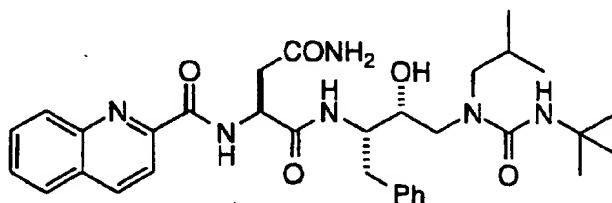
or other pharmaceutically acceptable salt thereof.

5 In another embodiment of this invention, the HIV protease inhibitor is



or pharmaceutically acceptable salt thereof.

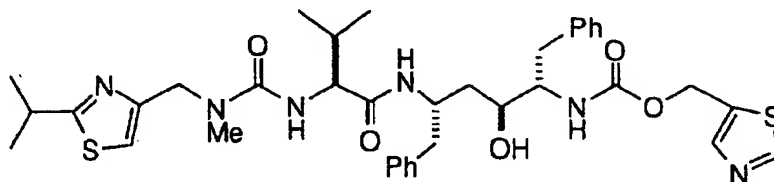
10 In another embodiment of this invention, the HIV protease inhibitor is



or pharmaceutically acceptable salt thereof.

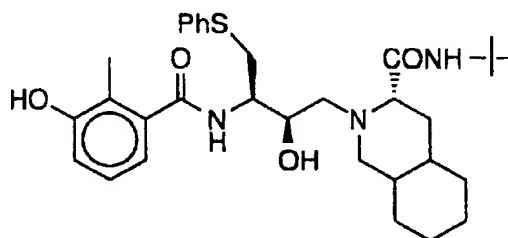
- 4 -

In another embodiment of the present invention, the HIV protease inhibitor is



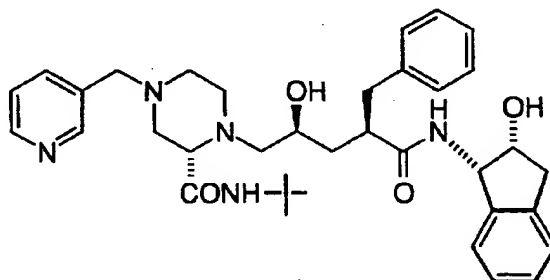
5 or pharmaceutically acceptable salt thereof.

In another embodiment of the present invention, the HIV protease inhibitor is



or pharmaceutically acceptable salts thereof.

10 One formulation of the present invention comprises, in each ml of formulation, about 20 mg sweetener, sufficient flavor, between about 50 mg (free base equivalent) and about 400 mg (free base equivalent), of the sulfate salt of

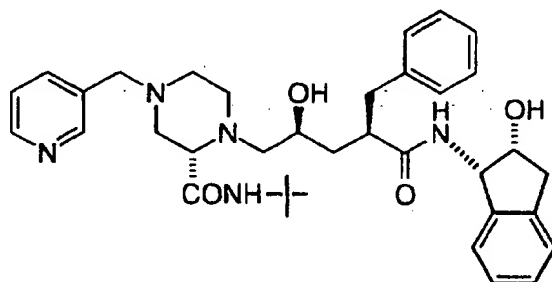


15 the residual volume being glycerol.

- 5 -

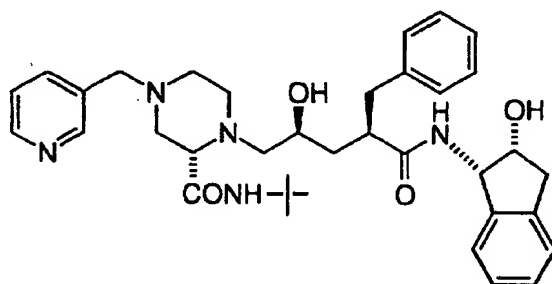
In one embodiment of the present invention, the preceeding formulation is limited to an amount of HIV protease inhibitor, in each ml of formulation, of between about 100 mg (free base equivalent) and about 300 mg (free base equivalent).

- 5 In another embodiment of the present invention, the formulation is limited to an amount of HIV protease inhibitor, in each ml of formulation, of between about 50 mg (free base equivalent) and about 400 mg (free base equivalent) of the sulfate salt of



- 10 the residual volume being glycerol.

In another embodiment of the present invention, the formulation is limited to an amount of HIV protease inhibitor, in each ml of formulation, of between about 100 mg (free base equivalent) and about 300 mg (free base equivalent) of the sulfate salt of



- 15

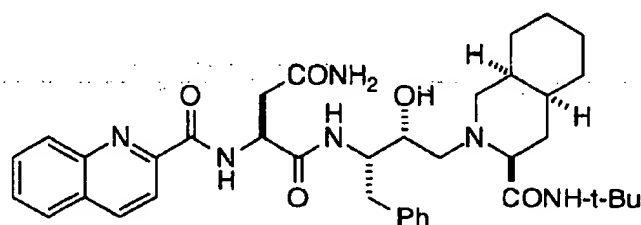
the residual volume being glycerol.

The pediatric formulations of the present invention include HIV protease inhibitors such as CRIVAN®, and Compounds I, II, III or IV.

- 6 -

The HIV protease inhibitor Compound CRIXIVAN<sup>®</sup> is synthesized by the protocol of Merck Case 18597Y, EP 0541168, published 12 May 1993, U.S. 5,413,999, herein incorporated by reference. CRIXIVAN<sup>®</sup> is the sulfate salt of N-(2(R)-hydroxy-1(S)-indanyl)-2(R)-phenylmethyl-4-(S)-hydroxy-5-(1-(4-(3-pyridylmethyl)-2(S)-N'-(t-butylcarboxamido)-piperazinyl))-pentaneamide.

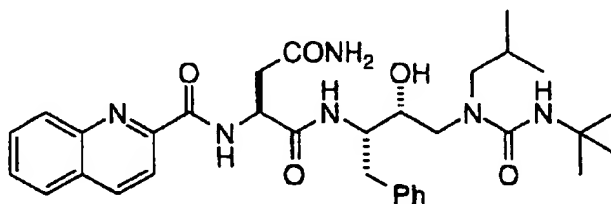
Compound I is:



10

or pharmaceutically acceptable salt thereof. It is synthesized by the procedures of EP 0346847. See also N.A. Roberts *et al.*, *Science*, **248**, 358 (1990).

Compound II is:



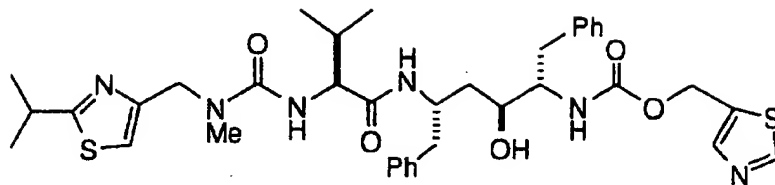
15

or pharmaceutically acceptable salt thereof. It is synthesized by the procedure of EP 0346847, PCT WO 92/08700 and PCT WO 92/8698.



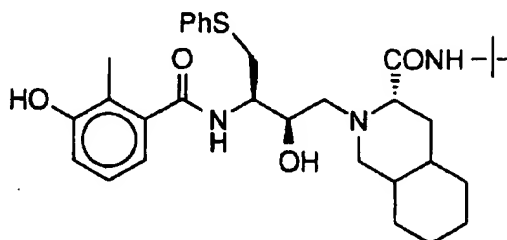
- 7 -

**Compound III is:**



or pharmaceutically acceptable salt thereof. It is synthesized by the  
5 methods of EP 0486948, and PCT WO 94/14436.

**Compound IV is:**



or pharmaceutically acceptable salts thereof. It is synthesized by the methods of WO 95/09843.

10           The pharmaceutically-acceptable salts of the present invention (in the form of water- or oil-soluble or dispersible products) include the conventional non-toxic salts or the quaternary ammonium salts which are formed, e.g., from inorganic or organic acids or bases. Examples of such acid addition salts include acetate, adipate, alginate, 15 aspartate, benzoate, benzenesulfonate, bisulfate, butyrate, citrate, camphorate, camphorsulfonate, cyclopentanepropionate, digluconate, dodecylsulfate, ethanesulfonate, fumarate, glucoheptanoate, glycerophosphate, hemisulfate, heptanoate, hexanoate, hydrochloride, hydrobromide, hydroiodide, 2-hydroxy-ethanesulfonate, lactate, 20 maleate, methanesulfonate, 2-naphthalenesulfonate, nicotinate, oxalate, pamoate, pectinate, persulfate, 3-phenylpropionate, picrate, pivalate, propionate, succinate, tartrate, thiocyanate, tosylate, and undecanoate. Base salts include ammonium salts, alkali metal salts such as sodium and

$$\hat{A}^{1/2} <^{1/2} \hat{a}$$

- 8 -

potassium salts, alkaline earth metal salts such as calcium and magnesium salts, salts with organic bases such as dicyclohexylamine salts, N-methyl-D-glucamine, and salts with amino acids such as arginine, lysine, and so forth. Also, the basic nitrogen-containing groups may be quaternized with such agents as lower alkyl halides, such as methyl, ethyl, propyl, and butyl chloride, bromides and iodides; dialkyl sulfates like dimethyl, diethyl, dibutyl; and diamyl sulfates, long chain halides such as decyl, lauryl, myristyl and stearyl chlorides, bromides and iodides, aralkyl halides like benzyl and phenethyl bromides and others. Other pharmaceutically acceptable salts include the sulfate salt ethanolate and sulfate salts.

C<sub>1-4</sub> alkyl esters as prodrugs are included wherever appropriate.

The pediatric formulation of the present invention is useful in the inhibition of HIV protease, the prevention or treatment of infection by human immunodeficiency virus (HIV) and the treatment of consequent pathological conditions such as AIDS, in children or infants. Treating AIDS or preventing or treating infection by HIV is defined as including, but not limited to, treating a wide range of states of HIV infection: AIDS, ARC (AIDS related complex), both symptomatic and asymptomatic, and actual or potential exposure to HIV. For example, the compounds of this invention are useful in treating infection by HIV after suspected past exposure to HIV by, e.g., blood transfusion, exchange of body fluids, bites, accidental needle stick, or exposure to patient blood during surgery.

### PREPARATION

In preparing the pediatric formulation, add the HIV protease inhibitor, or its pharmaceutically acceptable salt, to the glycerol with continuous stirring, taking care not to incorporate air into the system. Heating may be used to speed the dispersion process since it reduces the viscosity of the glycerol. However, raising the temperature

- 9 -

also increases the solubility of the drug in the glycerol and may potentate chemical incompatibility. Cooling the resulting solution apparently does not result in crystallization of the excess dissolved drug, although this may occur on long term storage.

5 For cases involving a drug rendered unstable by dissolution, it is desirable to minimize dissolution. For example, CRIXIVAN® has undesirable stability as a dissolved drug.

For the purposes of the pediatric formulations of the present invention, a suitable carrier is any non-toxic, high viscosity  
10 liquid, such as certain oils, e.g., glycerides, partial esters of glycerol, and mixtures thereof. Preferably, the carrier is a non-toxic, high viscosity, water-miscible liquid, such as glycerol.

Having dispersed the drug in glycerol or other carrier, flavors and sweeteners are then added with continuous stirring. The  
15 order of addition to drug of carrier, flavor or sweeteners can in principle be varied. In one preferred order, drug is first dispersed with glycerol or other carrier, then sweetener or flavor is added as needed. In another preferred order, sweetener and/or flavor are added first to glycerol, with heat to aid dissolution or dispersion, followed by addition  
20 of drug after cooling.

Another embodiment of the present invention is the dispersion in glycerol of drug, ie., an HIV protease inhibitor, without sweeteners or flavors. One preferred embodiment is the dispersion in glycerol of CRIXIVAN® without sweeteners or flavors.

25 The resulting dispersion should be deaerated, typically by applying a vacuum. After deaeration, the pediatric formulation may be packaged into a unit dose system, e.g., oral syringe, or into a multiple dose system, e.g, bottle with separate oral dosing syringe.

For CRIXIVAN®, dosing volumes of the pediatric  
30 formulation can vary from about 0.5 ml of a 100 mg/ml suspension to about 1.66 ml of a 300 mg/ml suspension or may reach higher volumes, e.g., 2.5 ml of a 200 mg/ml suspension. Dispersions of between about 50 mg/ml and about 400 mg/ml are feasible, but the range of between about 100 mg/ml and about 300 mg/ml is preferred.

- 10 -

The level of sweeteners is typically about 20 mg/ml dispersion of high intensity sweeteners, but may be higher for simple sugars such as sucrose. In principle any sweetener may be used.

Suitably high intensity sweeteners include but are not limited to

- 5 Magnasweet<sup>®</sup> (trademark of MAFCO), Acesulfame K, Aspartame or Saccharin. The actual level of sweetener can vary from effectively zero to about 300 mg/ml.

Suitable flavor systems include liquid flavors and flavors adsorbed onto solid substrate. Suitable pediatric flavors include but are  
10 not limited to bubble gum, cherry, and orange.

When administered orally as a suspension, the pediatric compositions may contain microcrystalline cellulose for imparting bulk, alginic acid or sodium alginate as a suspending agent, methylcellulose as a viscosity enhancer, and other

- 15 sweeteners/flavoring agents known in the art.

The formulations of this invention can be administered to humans in the dosage ranges specific for each compound.

CRIXIVAN<sup>®</sup> is administered orally in a dosage range between about 40 mg and about 4000 mg per day, divided into between one and

- 20 four doses per day. A preferred oral adult dosage range for CRIXIVAN<sup>®</sup> is between about 200 mg and about 1000 mg administered three times per day. A preferred oral pediatric dosage range for CRIXIVAN<sup>®</sup> is between about 50 mg and about 800 mg administered three times per day. Compound I or pharmaceutically  
25 acceptable salt thereof is administered orally at a dosage range of between about 100 mg and about 4000 mg per day. A preferred oral dosage range for Compound I or pharmaceutically acceptable salt thereof is between about 200 mg and about 1000 mg administered  
30 three times per day. Compound II is administered orally, e.g., as an elixir in 30% ethanol in water, at a dosage range of between about 100 mg and about 4000 mg per day. A preferred oral dosage range for Compound II is between about 200 mg and about 1000 mg administered three times per day. Compound III or pharmaceutically acceptable salt thereof is administered orally at a

- 11 -

- dosage range of between about 100 mg and about 4000 mg per day. A preferred oral dosage range for Compound III or pharmaceutically acceptable salt thereof is between about 200 mg and about 1000 mg administered three times per day. Compound IV or pharmaceutically acceptable salts thereof is administered orally as a dosage range of between about 100 mg and about 4000 mg per day. It will be understood, however, that the specific dose level and frequency of dosage for any particular patient may be varied and will depend upon a variety of factors including the activity of the specific compound employed, the metabolic stability and length of action of that compound, child vs. adult, the age, body weight, general health, sex, diet, mode and time of administration, rate of excretion, drug combination, the severity of the particular condition, and the host undergoing therapy.
- The formulations that follow are scaled to 1 ml quantities. Suitable scale up for manufacturing conditions is apparent to the skilled artisan.

#### EXAMPLE 1

- |                   |                               |
|-------------------|-------------------------------|
| CRIXIVAN®         | 100 mg (free base equivalent) |
| Magnasweet®       | 20 mg                         |
| Bubble gum flavor | q.s.                          |
| glycerol          | to 1 ml                       |
- Disperse CRIXIVAN® in glycerol with continuous stirring, without incorporating air into the system. Sweetener Magnasweet® and bubble gum flavor are then added with continuous stirring. Dearate and package.

#### EXAMPLE 2

- |                   |                               |
|-------------------|-------------------------------|
| CRIXIVAN®         | 200 mg (free base equivalent) |
| Magnasweet®       | 20 mg                         |
| Bubble gum flavor | q.s.                          |

- 12 -

glycerol to 1 ml

Disperse sweetener Magnasweet® and bubble gum flavor in glycerol, without incorporating air into the system. Add CRIXIVAN® with continuous stirring. Dearate and package.

5

### EXAMPLE 3

CRIXIVAN®	200 mg (free base equivalent)
Aspartame	20 mg
10 Cherry flavor	q.s.
glycerol	to 1 ml

Disperse CRIXIVAN® in glycerol with continuous stirring, without incorporating air into the system. Aspartame sweetener and  
15 cherry flavor are then added with continuous stirring. Dearate and package.

### EXAMPLE 4

20 CRIXIVAN®	200 mg (free base equivalent)
Saccharin	20 mg
Orange flavor	q.s.
glycerol	to 1 ml

25 Disperse CRIXIVAN® in glycerol with continuous stirring, without incorporating air into the system. Saccharin sweetener and orange flavor are then added with continuous stirring. Dearate and package.

30

### EXAMPLE 5

Compound I	150 mg
Saccharin	20 mg
Orange flavor	q.s.

- 13 -

glycerol to 1 ml

Disperse Compound I in glycerol with continuous stirring, without incorporating air into the system. Saccharin sweetener and orange flavor are then added with continuous stirring. Dearate and  
5 package.

#### EXAMPLE 6

Compound II	150 mg
10 Saccharin	20 mg
Orange flavor	q.s.
Glycerol	to 1 ml

Disperse Compound II in glycerol with continuous stirring, without incorporating air into the system. Saccharin sweetener and orange flavor are then added with continuous stirring. Dearate and  
15 package.

#### EXAMPLE 7

20 Compound III	150 mg
Aspartame	20 mg
Cherry flavor	q.s.
Glycerol	to 1 ml

Disperse Compound III in glycerol with continuous stirring, without incorporating air into the system. Aspartame sweetener and cherry flavor are then added with continuous stirring. Dearate and package.  
25

30

- 14 -

EXAMPLE 8

	Compound IV	150 mg
	Acesulfame K	3 mg
5	Bubble gum flavor	q.s.
	Glycerol	to 1 ml

Disperse Compound IV in glycerol with continuous stirring, without incorporating air into the system. Acesulfame K  
10 sweetener and bubble gum flavor are then added with continuous stirring. Dearate and package.

While the foregoing specification teaches the principles of  
the present invention, with examples provided for the purpose of  
15 illustration, it will be understood that the practice of the invention  
encompasses all of the usual variations, adaptations, modifications,  
deletions or additions of procedures and protocols described herein, as  
come within the scope of the following claims and its equivalents.



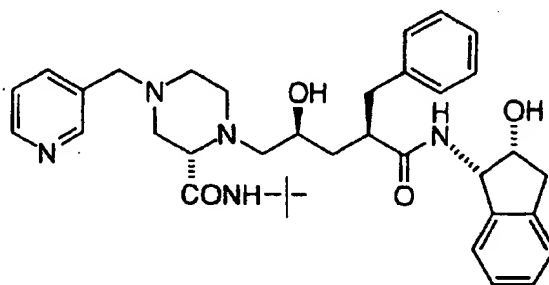
- 15 -

WHAT IS CLAIMED IS:

1. A pediatric formulation of an HIV protease inhibitor  
dispersed or suspended in a non-toxic, high viscosity, water-miscible  
5 liquid, to improve palatability.

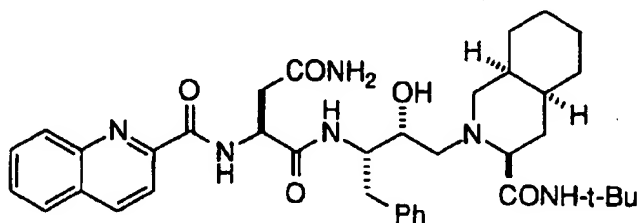
2. The pediatric formulation of claim 1, wherein the  
liquid is glycerol.

10 3. The formulation of Claim 1 or 2, wherein the HIV  
protease inhibitor is the sulfate salt of



or other pharmaceutically acceptable salt thereof.

15 4. The formulation of Claim 1 or 2, wherein the HIV  
protease inhibitor is

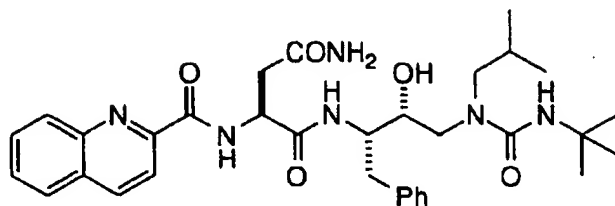


or pharmaceutically acceptable salt thereof.

20

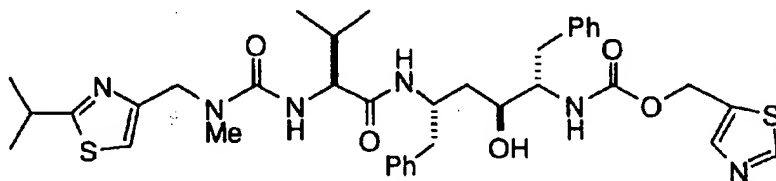
- 16 -

5. The formulation of Claim 1 or 2, wherein the HIV protease inhibitor is



5 or pharmaceutically acceptable salt thereof.

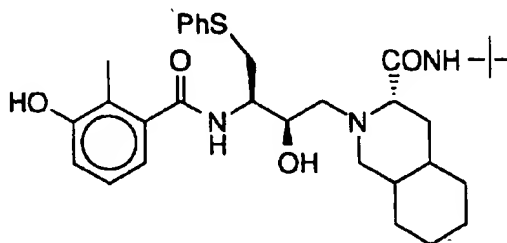
6. The formulation of Claim 1 or 2, wherein the HIV protease inhibitor is



10

or pharmaceutically acceptable salt thereof.

7. The formulation of Claim 1 or 2, wherein the HIV protease inhibitor is

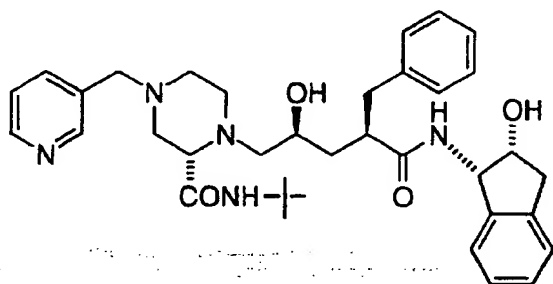


15

or pharmaceutically acceptable salts thereof.

- 17 -

8. The formulation of Claim 2, comprising, in each ml, about 20 mg sweetener, sufficient flavor, between about 50 mg (free base equivalent) and about 400 mg (free base equivalent), of the sulfate salt of

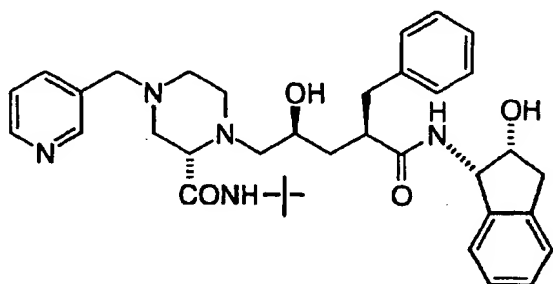


5

the residual volume being glycerol.

9. The formulation of Claim 8, wherein the amount of HIV protease inhibitor in each ml of formulation is between about 100 mg (free base equivalent) and about 300 mg (free base equivalent).

10. The formulation of Claim 2, comprising, in each ml, between about 50 mg (free base equivalent) and about 400 mg (free base equivalent) of the sulfate salt of



15

the residual volume being glycerol.

- 18 -

11. The formulation of Claim 10, wherein the amount of HIV protease inhibitor in each ml of formulation is between about 100 mg (free base equivalent) and about 300 mg (free base equivalent).

# INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 97/09109

## A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 A61K9/08 A61K9/10 A61K47/10 A61K38/04 A61K38/06  
A61K9/00

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0 346 847 A (HOFFMANN LA ROCHE) 20 December 1989 cited in the application * p.13, 1.47 & claims *	1,2,4
Y	* p.13, 1.35-55 *	3,5-11
	---	
X	WO 95 20384 A (ABBOTT LAB) 3 August 1995 see claims 1-24	1,6
Y	see the whole document	3-11
	---	
X	US 5 296 604 A (HANKO RUDOLF H ET AL) 22 March 1994 * col.6, 1.65-66; claim 12 *	1,2
Y	see the whole document	3-11
	---	
	-/--	



Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

### \* Special categories of cited documents :

- \*A\* document defining the general state of the art which is not considered to be of particular relevance
- \*E\* earlier document but published on or after the international filing date
- \*L\* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- \*O\* document referring to an oral disclosure, use, exhibition or other means
- \*P\* document published prior to the international filing date but later than the priority date claimed

- \*T\* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- \*X\* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- \*Y\* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- \*Z\* document member of the same patent family

Date of the actual completion of the international search

26 September 1997

Date of mailing of the international search report

14. 10. 97

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2  
NL - 2280 HV Rijswijk  
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,  
Fax: (+31-70) 340-3016

Authorized officer

Uiber, P

# INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 97/09109

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	EP 0 441 307 A (SHOWA PHARM CHEM IND) 14 August 1991 * p.1, 1.27-37; claims 1-4 * -----	3-11

# INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 97/09109

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 0346847 A	20-12-89	AU 624144 B	04-06-92
		AU 3613089 A	14-12-89
		DE 68915207 D	16-06-94
		DE 68915207 T	18-08-94
		ES 2052815 T	16-07-94
		FI 95693 B	30-11-95
		HR 930443 A	31-12-96
		IE 64495 B	09-08-95
		IL 90550 A	25-01-94
		JP 2042048 A	13-02-90
		JP 2515019 B	10-07-96
		KR 9705905 B	22-04-97
		NO 175715 B	15-08-94
		PT 90836 B	30-11-94
		US 5157041 A	20-10-92
		US 5554756 A	10-09-96
WO 9520384 A	03-08-95	US 5652369 A	29-07-97
		US 5620987 A	15-04-97
		US 5446161 A	29-08-95
US 5296604 A	22-03-94	AU 1524895 A	15-08-95
		CA 2178632 A	03-08-95
		EP 0732923 A	25-09-96
		US 5484801 A	16-01-96
EP 0441307 A	14-08-91	NONE	
		JP 2107954 C	06-11-96
		JP 3232816 A	16-10-91
		JP 7014872 B	22-02-95
		CA 2035693 A,C	07-08-91
		DE 69104079 D	27-10-94
		DE 69104079 T	13-04-95
		US 5154926 A	13-10-92

